Effect of Metformin Versus Placebo on New Primary Cancers in Canadian Cancer Trials Group MA.32: A Secondary Analysis of a Phase III Randomized Double-Blind Trial in Early Breast Cancer

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DOI https://doi.org/10.1200/JCO.23.00296

ABSTRACT

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned coprimary or secondary analyses are not yet available. Clinical trial updates provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.

Metformin has been associated with lower cancer risk in epidemiologic and preclinical research. In the MA.32 randomized adjuvant breast cancer trial, metformin (*v* placebo) did not affect invasive disease-free or overall survival. Here, we report metformin effects on the risk of new cancer. Between 2010 and 2013, 3,649 patients with breast cancer younger than 75 years without diabetes with high-risk T1-3, N0-3 M0 breast cancer (any estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2) were randomly assigned to metformin 850 mg orally twice a day or placebo twice a day for 5 years. New primary invasive cancers (outside the ipsilateral breast) developing as a first event were identified. Time to events was described by the competing risks method; two-sided likelihood ratio tests adjusting for age, BMI, smoking, and alcohol intake were used to compare metformin versus placebo arms. A total of 184 patients developed new invasive cancers: 102 metformin and 82 placebo, hazard ratio (HR), 1.25; 95% CI, 0.94 to 1.68; $P = .13$. These included 48 contralateral invasive breast cancers (27 metformin *v* 21 placebo), HR, 1.29; 95% CI, 0.72 to 2.27; $P = .40$ and 136 new nonbreast primary cancers (75 metformin *v* 61 placebo), HR, 1.24; 95% CI, 0.88 to 1.74; $P = .21$. Metformin did not reduce the risk of new cancer development in these nondiabetic patients with breast cancer.

ACCOMPANYING CONTENT

Appendix

Protocol

Accepted July 20, 2023

Published September 11, 2023

J Clin Oncol 41:5356-5362

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INTRODUCTION

Metformin, a biguanide commonly used to treat type 2 diabetes, has been associated with lower overall cancer risk in epidemiologic studies conducted in patients with diabetes.[1,2] Meta-analyses of these studies have inconsistently identified lower risk of some types of cancer when individuals receive metformin.[3-14] It has been suggested that data from observational studies of metformin and cancer risk seem largely unreliable, studies using designs least likely to be affected by bias (notably selection and time-related biases) being most likely to yield results that did not support a causal effect of metformin on cancer risk.[15-17] The Diabetes Prevention Program trial, which randomly assigned adults with prediabetes to metformin, a lifestyle-based weight loss intervention or placebo, reported no effect of metformin versus placebo on cancer mortality at 21-year follow-up (hazard ratio [HR], 1.04; 95% CI, 0.72 to 1.52; $P = .83$).[18]

Current understanding of metformin action includes systemic effects resulting from reduced insulin signaling through PI3K/RAS pathways and cancer cell direct effects (notably LKB1–mediated activation of AMPK, a negative regulator of PI3K/Akt/mTOR signaling and protein synthesis). Some preclinical research suggests that metformin may lower cancer risk; however, translation to the clinical setting is not straightforward.[19,20]

Here, we report the effect of metformin versus placebo on new invasive cancers in MA.32, a phase III adjuvant randomized trial of metformin versus placebo in high-risk T1-3, N0-2, M0 breast cancer. We have previously reported

TABLE 1. Baseline Patient and Tumor Characteristics

Characteristic	Metformin (n = 1,824)	Placebo (n = 1,825)	Total (N = 3,649)
Age, years			
Mean (SD)	52.2 (10.1)	52.6 (10.1)	52.4 (10.1)
BMI, kg/m^2			
Mean (SD)	28.7 (6.6)	28.5 (6.2)	28.6 (6.4)
Sex, No. (%)			
Female	1,821 (99.8)	1,822 (99.8)	3,543 (99.8)
Male	3 (0.2)	3 (0.2)	6 (0.2)
Race, No. (%)			
Asian	51 (2.8)	48 (2.6)	99 (2.7)
Black or African American	83 (4.6)	84 (4.6)	167 (4.6)
America Indian or Alaska Native	9 (0.5)	8 (0.4)	17 (0.5)
Native Hawaiian or Pacific Islander	5 (0.3)	8 (0.4)	13 (0.4)
Non-Hispanic White	1,569 (86.0)	1,557 (85.3)	3,126 (85.7)
Hispanic	84 (4.6)	94 (5.2)	178 (4.9)
Smoking history, No. (%)			
Current smoker	151 (8.3)	142 (7.8)	293 (8.0)
Past smoker	793 (43.5)	756 (41.4)	1,549 (42.4)
Never-smoker	880 (48.2)	927 (50.8)	1,807 (49.5)
Current alcohol consumption, No. (%)			
Yes	1,231 (72.4)	1,320 (72.3)	2,641 (72.4)
No	503 (27.6)	505 (27.7)	1,008 (27.6)
Not reported (or refused) or unknown	23 (1.3)	26 (1.4)	49 (1.3)
Menopausal status, No. (%)			
Premenopausal[a]	714 (39.1)	698 (38.2)	1,412 (38.7)
Postmenopausal[b]	1,110 (60.1)	1,127 (61.8)	2,237 (61.3)
T stage, No. (%)			
T1	620 (34.0)	619 (33.9)	1,239 (34.0)
T2	969 (53.1)	974 (53.4)	1,943 (53.2)
T3	234 (12.8)	232 (12.7)	466 (12.1)
T4	1 (0.0)	0 (0.0)	1 (0.0)
N stage, No. (%)			
N0+N0 (i+)	791 (43.3)	821 (45.0)	1,612 (44.2)
N1+N1mi	724 (39.7)	703 (38.5)	1,427 (39.1)
N2	212 (11.6)	210 (11.5)	422 (11.6)
N3	97 (5.3)	91 (5.0)	188 (5.2)
ER/PgR receptor status, No. (%)			
Positive	1,268 (69.5)	1,265 (69.3)	2,533 (69.4)
Negative	556 (30.5)	560 (30.7)	1,116 (30.6)
HER2 status, No. (%)			
Negative	1,510 (82.8)	1,519 (83.2)	3,029 (83.0)
Positive	314 (17.2)	306 (16.8)	620 (17.2)
Histologic grade, No. (%)			
Grade 1 (low)	170 (9.3)	160 (8.8)	330 (9.0)
Grade 2 (intermediate)	644 (35.3)	645 (35.3)	1,289 (35.3)
Grade 3 (high)	996 (54.6)	998 (54.7)	1,994 (54.6)
Missing/unknown	14 (0.8)	22 (1.2)	36 (1.0)
Adjuvant radiotherapy, No. (%)			
No	491 (26.9)	455 (24.9)	946 (25.9)
Yes	1,333 (73.1)	1,370 (75.1)	2,703 (74.1)

(continued on following page)

TABLE 1. Baseline Patient and Tumor Characteristics (continued)

Characteristic	Metformin (n = 1,824)	Placebo (n = 1,825)	Total (N = 3,649)
Adjuvant chemotherapy, No. (%)			
No	196 (10.7)	195 (10.7)	391 (10.7)
Yes	1,628 (89.3)	1,630 (17.3)	3,258 (89.3)
Adjuvant hormone therapy, No. (%)			
None	700 (38.4)	705 (38.6)	1,405 (38.5)
Tamoxifen	607 (33.3)	624 (34.2)	1,231 (33.7)
Aromatase inhibitor	517 (28.3)	496 (27.2)	1,013 (27.8)
Adjuvant trastuzumab, No. (%)			
No	1,510 (82.8)	1,510 (82.7)	3,020 (82.8)
Yes	314 (17.2)	315 (17.3)	629 (17.2)

Abbreviations: ECOG, Eastern Cooperative Oncology group; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; N, nodal; PgR, progesterone receptor; SD, standard deviation; T, tumor.

[a]Premenopausal: <6 months since last menses and no bilateral oophorectomy OR does not meet postmenopausal criteria and younger than 50 years.

[b]Postmenopausal: prior bilateral oophorectomy or >12 months since last menses OR does not meet premenopausal criteria and older than 50 years.

the absence of an effect of metformin on invasive disease-free survival (IDFS) or overall survival in hormone receptor–positive or hormone receptor–negative breast cancer.[21] Exploratory analyses suggested beneficial effects in human epidermal growth factor receptor 2 (HER2)–positive breast cancer, notably in those with at least one C allele of the rs11212617 single-nucleotide polymorphism (SNP), a SNP associated with enhanced glycemic response and higher metformin blood levels in patients with diabetes.[22,23]

METHODS

Detailed methods have been reported previously.[21] Briefly, this investigator-initiated phase III randomized trial recruited patients (2010-2013) age 18-74 years, receiving standard therapy for a high-risk T1-3, N0-3, M0 breast cancer (excluding T1abN0) and diagnosed during the previous year. Exclusions included fasting glucose >7.0 mmol/L, history of diabetes or lactic acidosis, current use of diabetes medication, previous recurrence or other invasive cancer, intake of ≥3 alcoholic drinks daily, or marked organ dysfunction. Random assignment (to metformin 850 mg orally twice a day or placebo orally twice a day for 5 years) was stratified for (1) estrogen receptor and/or progesterone receptor positive (≥1%) versus both negative (<1%), (2) BMI ≤30 kg/m² versus >30 kg/m², (3) HER2 positive versus negative, and (4) any versus no adjuvant chemotherapy. In 2016, after a second interim analysis, futility was declared in hormone receptor–negative patients; study drug was discontinued in this group after a median exposure of 36.7 months, but blinded follow-up and event ascertainment continued.

Our current focus was a secondary analysis of new primary invasive cancers in the contralateral breast (a protocol-specified secondary outcome) and exploratory analyses of new cancers elsewhere and overall (ipsilateral breast events were considered recurrences) that occurred as first IDFS events, with an exploration of whether effects of metformin differed by baseline BMI, insulin, glucose, homeostasis model assessment (HOMA, reflecting insulin resistance, calculated as glucose [mg/dL] × insulin [pmol/L]/22.5),[24] leptin and highly sensitive C-reactive protein (hsCRP) as well as smoking, rs11212617 SNP status, and receipt of adjuvant hormone therapy. Time to new cancer was analyzed by the competing risks method[25]; two-sided likelihood ratio tests adjusting for age, BMI, smoking (ever *v* never smoked), and alcohol (any *v* no intake during the past year), with other IDFS events as competing risk and censoring at the last follow-up without an IDFS event, were performed. MA.32 was approved by the Adult Central Institutional Review Board (National Institutes of Health) and institutional review boards of the participating institutions. Patients provided written informed consent to participate.

RESULTS

We randomly assigned 3,649 patients; all were included in intent-to-treat analyses. Baseline subject, tumor, and treatment characteristics were well balanced between study arms (Table 1). The median follow-up and drug exposure were 95.9 (range, 0-121) months and 58.8 months, respectively.

There were 184 new primary cancers reported as a first IDFS event, 102 on the metformin arm and 82 on the placebo arm (HR, 1.25; 95% CI, 0.94 to 1.68; $P = .13$; Fig 1). Forty-eight were contralateral invasive breast cancers (27 metformin arm, 21 placebo arm), HR, 1.29 (95% CI, 0.72 to 2.27; $P = .40$), and 136 were nonbreast invasive cancers (75 metformin, 61 placebo), HR 1.24 (95% CI, 0.88 to 1.74; $P = .21$). The most common nonbreast cancers were gynecological (n = 31), lung (n = 26), hematological (n = 23), GI

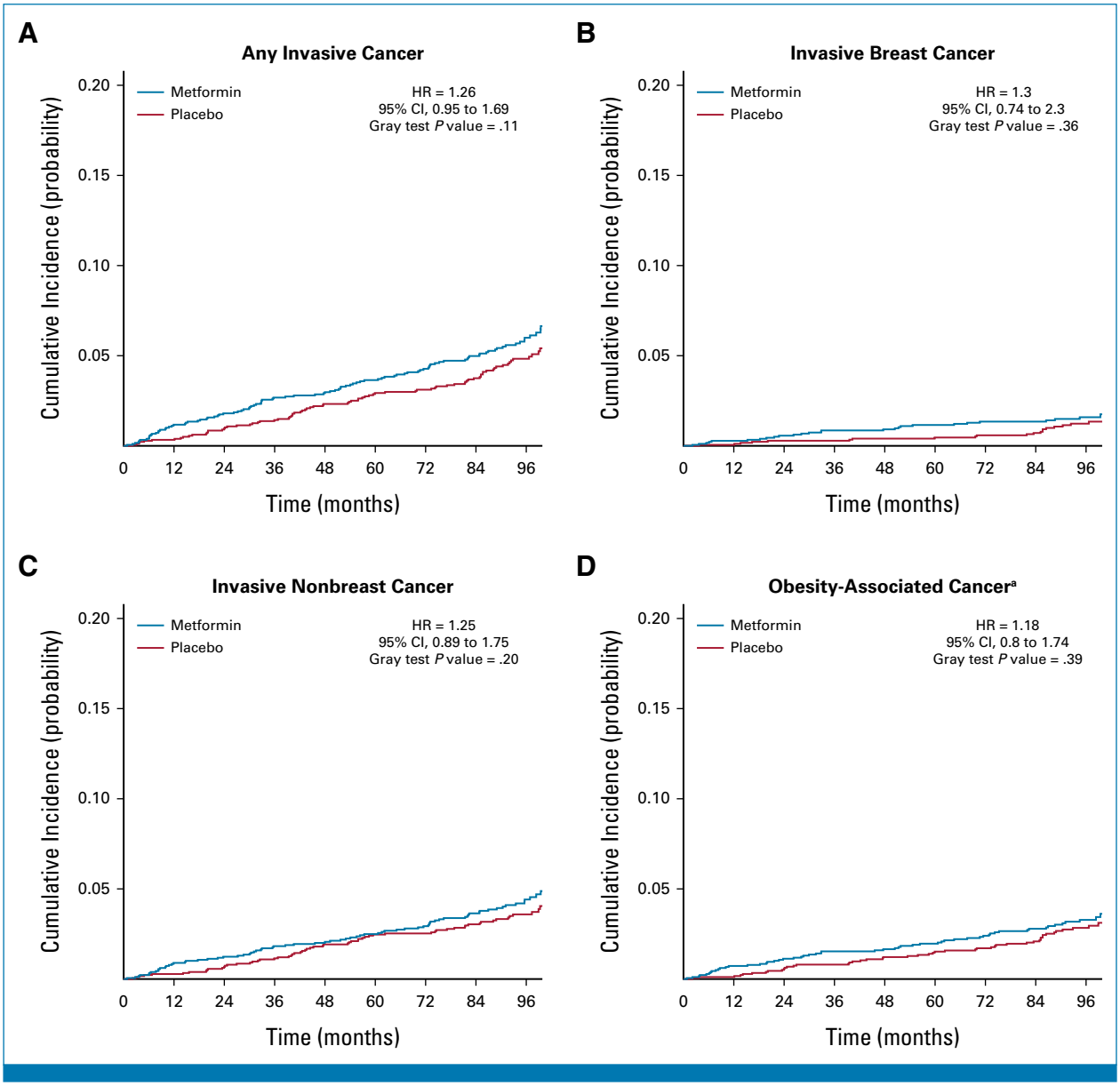

FIG 1. Cumulative incidence curves with respect to metformin and placebo for (A) any invasive cancer, (B) invasive breast cancer, (C) nonbreast invasive cancer, and (D) obesity-associated cance. [a]Obesity-associated cancers include invasive breast, colorectal, pancreatic, gastric cardia, ovary, uterus, kidney, thyroid, and myeloma. HR, hazard ratio.

(n = 17), and melanoma (n = 13; Appendix Table A1, online only). The effect of metformin versus placebo on the risk of developing a new invasive cancer did not differ by hormone receptor status (positive HR, 1.19[95% CI, 0.83 to 1.69] *v* negative HR, 1.44 [95% CI, 0.86 to 2.41]) or HER2 status (positive HR, 0.83 [95% CI, 0.39 to 1.81] *v* negative HR, 1.36 [95% CI, 0.99 to 1.86]) of the primary tumor (interaction *P* values .53 and .25, respectively) or by receipt of adjuvant hormonal therapy (tamoxifen HR, 1.23 [95% CI, 0.73 to 2.08]; aromatase inhibitor HR, 1.34 [95% CI, 0.80 to 2.24]; none HR, 1.21 [95% CI, 0.75 to 1.95; interaction *P* value .96). Metformin effects were similar for obesity-associated cancers (invasive breast, colorectal, pancreatic, gastric cardia, ovary, uterus, kidney, thyroid, and myeloma)[26] and other cancers (HR, 1.18; 95% CI, 0.81-1.74; $P = .39$ and HR, 1.37; 95% CI, 0.88 to 2.13; $P = .16$, respectively) and for tobacco-associated (lung, head and neck, kidney, and bladder) and other cancers (HR, 1.77; 95% CI, 0.87 to 3.60; $P = .11$ and HR, 1.18; 95% CI, 0.85 to 1.62; $P = .32$). The effects of metformin did not differ by baseline levels of BMI (<25, 25-30, >30); quartiles of insulin, HOMA, leptin, and hsCRP; smoking (never, ever); and rs11212617 SNP status (any C *v* AA genotype; Table 2). Ten patients developed contralateral ductal carcinoma in situ (eight metformin, two placebo); when these were included as

TABLE 2. Effect of Metformin Versus Placebo on Cancer Risk in Relation to BMI, Metabolic Factors, Smoking, and rs11212617 SNP Status, With (unadjusted) HRs and Interaction *P* Values

	Any Invasive Cancer (n = 184 events)	Invasive Breast Cancer (n = 48 events)	Invasive Nonbreast Cancer (n = 136 events)	Obesity-Associated Cancer[a] (n = 104 events)
Characteristic	Met *v* Placebo, HR (95% CI)	Met *v* Placebo, HR (95% CI)	Met *v* Placebo, HR (95% CI)	Met *v* Placebo, HR (95% CI)
BMI				
<25 kg/m^2 (n = 1,174)	1.17 (0.67 to 2.05)	2.06 (0.52 to 8.14)	1.03 (0.56 to 1.91)	1.13 (0.50 to 2.55)
25-30 kg/m^2 (n = 1,206)	1.01 (0.60 to 1.69)	1.17 (0.39 to 3.47)	0.97 (0.54 to 1.73)	1.30 (0.65 to 2.62)
>30 kg/m^2 (n = 1,269)	1.57 (1.00 to 2.49)	1.17 (0.54 to 2.52)	1.83 (1.03 to 3.25)	1.13 (0.65 to 2.00)
Intx *P*	.43	.76	.24	.94
Insulin				
Q1 (0 to <41, n = 864)	1.17 (0.63 to 2.16)	1.42 (0.31 to 6.52)	1.12 (0.57 to 2.19)	0.91 (0.38 to 2.19)
Q2 (41 to <60, n = 843)	0.98 (0.54 to 1.77)	1.13 (0.38 to 3.36)	0.92 (0.46 to 1.86)	0.98 (0.41 to 2.34)
Q3 (69 to <95, n = 886)	1.77 (0.86 to 3.64)	1.67 (0.48 to 5.84)	1.80 (0.75 to 4.34)	2.24 (0.84 to 5.94)
Q4 (95+, n = 886)	1.43 (0.80 to 2.57)	1.34 (0.47 to 3.82)	1.46 (0.72 to 2.96)	1.13 (0.57 to 2.26)
Intx *P*	.60	.98	.62	.51
HOMA				
Q1 (0 to <1.26, n = 634)	1.12 (0.55 to 2.26)	1.17 (0.23 to 5.80)	1.10 (0.50 to 2.40)	0.92 (0.35 to 2.47)
Q2 (1.26 to <1.91, n = 632)	0.68 (0.34 to 1.37)	1.00 (0.20 to 4.90)	0.62 (0.28 to 1.37)	0.62 (0.21 to 1.89)
Q3 (1.91 to <3.03, n = 640)	1.28 (0.62 to 2.64)	0.82 (0.25 to 2.69)	1.67 (0.66 to 4.26)	1.08 (0.46 to 2.54)
Q4 (3.03+, n = 635)	1.53 (0.79 to 2.96)	1.84 (0.47 to 7.32)	1.42 (0.67 to 3.03)	1.09 (0.49 to 2.42)
Intx *P*	.39	.85	.34	.86
Leptin				
Q1 (0 to <6.38, n = 873)	1.09 (0.59 to 2.02)	1.11 (0.22 to 5.63)	1.09 (0.56 to 2.11)	1.01 (0.39 to 2.63)
Q2 (6.38 to <12.64, n = 881)	1.18 (0.62 to 2.23)	2.21 (0.58 to 8.43)	0.95 (0.45 to 2.00)	1.12 (0.50 to 2.51)
Q3 (12.64 to <22.03, n = 870)	1.33 (0.75 to 2.37)	1.72 (0.58 to 5.13)	1.20 (0.61 to 2.36)	1.09 (0.52 to 2.29)
Q4 (22.03+, n = 871)	1.53 (0.87 to 2.70)	0.80 (0.30 to 2.15)	2.11 (1.03 to 4.35)	1.36 (0.66 to 2.80)
Intx *P*	.86	.61	.41	.96
hs-CRP				
Q1 (0 to < 0.5, n = 777)	0.93 (0.46 to 1.88)	4.17 (0.45 to 38.9)	0.73 (0.34 to 1.57)	1.58 (0.56 to 4.49)
Q2 (0.5 to <1.3, n = 918)	0.94 (0.48 to 1.82)	0.40 (0.07 to 2.05)	1.15 (0.55 to 2.42)	0.75 (0.32 to 1.78)
Q3 (1.3 to <3.2, n = 902)	1.32 (0.78 to 2.22)	2.26 (0.79 to 6.50)	1.07 (0.58 to 1.97)	1.26 (0.61 to 2.61)
Q4 (3.2+, n = 898)	1.90 (1.08 to 3.37)	0.99 (0.40 to 2.48)	2.78 (1.29 to 6.00)	1.25 (0.64 to 2.46)
Intx *P*	.31	.16	.07	.68
Smoking history				
Never-smoker	1.36 (0.89 to 2.07)	1.51 (0.67 to 3.39)	1.30 (0.80 to 2.13)	1.33 (0.79 to 2.23)
Ever smoker	1.19 (0.79 to 1.78)	1.08 (0.50 to 2.48)	1.21 (0.76 to 1.94)	1.02 (0.57 to 1.83)
Intx *P*	.65	.59	.84	.51
rs11212617				
Any C	1.22 (0.85 to 1.76)	1.34 (0.64 to 2.83)	1.17 (0.78 to 1.80)	1.23 (0.75 to 2.02)
AA	1.53 (0.86 to 2.74)	1.17 (0.43 to 3.24)	1.71 (0.84 to 3.51)	1.10 (0.53 to 2.27)
Intx *P*	.52	.84	.37	.80

Abbreviations: HOMA, homeostasis model assessment; HR, hazard ratio; hs-CRP, highly sensitive C-reactive protein; Intx *P*, interaction *P* value; Met, metformin; Q, quartile; SNP, single-nucleotide polymorphism.

[a]Obesity-associated cancers were those categorized as having sufficient evidence of a link between body fatness and increased cancer risk by Lauby-Secretan et al.[26] These included GI (colorectal, gastric cardia, pancreatic), gynecologic (uterus, ovarian), and postmenopausal breast, kidney, thyroid, and myeloma.

cancers, the HR for metformin versus placebo for any breast cancer was 1.35 (95% CI, 0.77 to 2.37; $P = .30$) and for any cancer was 1.28 (95% CI, 0.95 to 1.70; $P = .10$).

DISCUSSION

The MA.32 trial provided a unique opportunity to examine the effects of metformin on the risk of developing new primary invasive cancers in a population without diabetes. Metformin did not affect the risk of new contralateral breast cancer, any invasive cancer, cancers outside of the breast, obesity, or tobacco-associated cancers. Point estimates of risk were all above 1, making it unlikely that additional power would have identified a clinically important reduction in risk. Furthermore, metformin did not reduce cancer risk in subgroups defined by BMI, metabolic factors (insulin, HOMA, leptin, hsCRP), smoking history, or rs11212617 SNP status, factors that could potentially be associated with metformin benefit.

It is unclear whether our results are generalizable to populations with diabetes or prediabetes. Because of its beneficial physiologic effect, it is possible that metformin could reduce cancer risk in populations experiencing hyperglycemia, hyperinsulinemia, or inflammation. However, results of the Diabetes Prevention Program[18] and critical appraisals of the observational studies in populations with diabetes[1–17] discussed above raise concern about metformin benefit.

These findings do not support the use of metformin to reduce risk of new primary cancers in patients without diabetes who have high-risk breast cancer.

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DISCLAIMER

The study sponsors have no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; and the decision to submit the manuscript for publication.

SUPPORT

Supported by the Canadian Cancer Society Research Institute (No. 021039); National Cancer Institute (US; Nos. CA077202, CA180868, CA180822); The Breast Cancer Research Foundation (New York); Canadian Breast Cancer Foundation—Ontario Region, Ontario Institute for Cancer Research (No. 10NOV-467); Apotex Canada (in kind donation of placebo and metformin); and Hold'em for Life Charity.

CLINICAL TRIAL INFORMATION

NCT01101438

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.23.00296.

DATA SHARING STATEMENT

The primary efficacy analysis will be available from the Canadian Cancer trials Group (Kingston, ON). The associated data have been uploaded to the NCI data archive website: http//nctn-data-archive.nci.nih.gov/view-trials and will be searchable via ClinicalTrials.gov identifier (NCT1101438). Further information regarding that analysis and the data analyzed in this substudy can be obtained from the corresponding author.

AUTHOR CONTRIBUTIONS

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Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Effect of Metformin Versus Placebo on New Primary Cancers in Canadian Cancer Trials Group MA.32: A Secondary Analysis of a Phase III Randomized Double-Blind Trial in Early Breast Cancer

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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Research Funding: Epic Sciences (Inst)

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Honoraria: AstraZeneca, Merck Sharp & Dohme, Seagen, Novartis Canada Pharmaceuticals Inc, Pfizer, Lilly, Gilead Sciences
Consulting or Advisory Role: Pfizer, Novartis, Astrazeneca, Merck, Lilly, Roche, Mylan, Ayala Pharmaceuticals, Gilead Sciences
Research Funding: Pfizer (Inst), Bristol Myers Squibb (Inst), AstraZeneca (Inst)
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Research Funding: Imagia
Patents, Royalties, Other Intellectual Property: Patent related to health

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Stock and Other Ownership Interests: AstraZeneca
Consulting or Advisory Role: AstraZeneca, Lilly, Genentech, Macrogenics, Pfizer, Seagen, Sanofi
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Travel, Accommodations, Expenses: Pfizer, Daiichi Sankyo, eisai, Novartis

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. New Invasive Cancers Reported as a First Invasive Disease-Free Survival Event

Cancer	Metformin, No.	Placebo, No.	Total, No.
Any invasive cancer	102	82	184
Breast	27	21	48
Brain	2	0	2
GI			
Pancreatic	2	1	3
Gastric cardia	3	0	3
Colorectal	6	5	11
Genitourinary			
Bladder	1	1	2
Kidney	1	1	2
Gynecological			
Fallopian tube	1	0	1
Ovarian	5	4	9
Uterus	8	9	17
Vaginal	1	0	1
Cervical	2	1	3
Head and neck	3	0	3
Hematological			
Leukemia	9	3	12
Lymphoma	1	6	7
Myeloma	1	3	4
Lung	16	10	26
Lymphoid disorder	1	0	1
Melanoma	5	8	13
Neuroendocrine	1	2	3
Peritoneum	1	0	1
Salivary gland	1	3	4
Thyroid	3	4	7
Unknown primary (adenocarcinoma)	1	0	1